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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,400	09/17/2001	Brian Andrew Hills	4040.000300	9184

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EXAMINER
HAGHIGHATIAN, MINA

ART UNIT	PAPER NUMBER
1616	11

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/856,400	Applicant(s) HILLS ET AL.	
	Examin r Mina Haghighatian	Art Unit 1616	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-37 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-37 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed 04/07/03 was entered. No claims were cancelled. Two new claims (claims 36 and 37) were added.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radhakrishnan et al (4,895,719) in view of Mautone (5,306,483) and further in view of Rubin et al (5,925,334).

Radhakrishnan teaches method and apparatus for administering dehydrated liposomes by inhalation. Disclosed is a liposome-based aerosol system for delivering a drug, at a controlled release rate, via the respiratory tract. Two discoveries are made, first, rapid systemic uptake of drugs from the site of administration in the respiratory tract can be eliminated or greatly reduced by administering the drug in a predominantly liposome-encapsulated form. Secondly, it was found that the rate of release of a water-soluble drug from a drug/liposome composition delivered to the respiratory tract can be modulated according to the acyl-chain composition of the phospholipids making up liposomes (col. 2, lines 55-68).

Radhakrishnan also teaches that administration of the $ß_2$–agonist metaproteranol sulfate (MPS) in liposomal form via inhalation reduced initial plasma levels of the drug

more than about 8 fold with respect to free drug, and that plasma levels remained substantially constant over a two hour period. Also disclosed is that $ß_2$–adrenoreceptor agonists, when administered in liposome-entrapped form at a therapeutic dose, produce significantly greater bronchodilation, over an extended time period, than is produced by the same amount of $ß_2$-agonist delivered to the respiratory tract in a free drug aerosol form (col. 3, lines 20-47).

Radhakrishnan discloses that the particles formed have a fine particle size, retain the majority of their originally encapsulated material, and are stable. The delivery device is a metered dose spray device designed to release a selected volume of the suspension in aerosolized form (col. 3, line 48 to col. 4, line 15).

Radhakrishnan teaches the effect of liposome lipid components on the rate of drug release in the respiratory tract, the combination of specific phospholipids and that the effect of lipid charge on drug release rates indicates that the addition of a negatively charged lipid, such as phosphatidylglycerol (PG) at a mole ratio of about 10%, produces a slight to moderate increase in efflux half life. Table 1 discloses some properties of phospholipids used in liposomes (col. 5, lines 5 to col. 6, line 68).

The pharmaceutically active agents suitable for the liposome preparations are listed in column 7, which include albuterol sulfate, terbutaline sulfate, atropine methyl nitrate, cromolyn sodium, beclomethasone, dexamethasone, etc. The said preparations contain particles optimally less than about 5 microns (col. 8, lines 30-53). Radhakrishnan also discloses the dosage for liposome and the drug in this combination

formulation and states that, for example, for delivering 1 mg of drug about 20 mg of liposome per aerosol dose is used (col. 12, lines 9-23).

Radhakrishnan lacks disclosure on high doses of phospholipids and on the weight ratios for the components.

Mautone teaches a process to prepare lipid crystalline figures in chloro or hydro fluorocarbon propellants or mixtures thereof for the aerosol delivery of therapeutically active substances. The acellular surface film of the lung, the so-called surfactant system, and the various phospholipids are described in columns 1 to 4. Also disclosed is that the vehicle system for the said invention can deliver for example 5 mg each of DPPC:CP, DPPC:PG or DPPC:CP:PG (200:1, 7:1 or 7:0.35:1, w/w, respectively), which when delivered quantitatively covers 100% of the airspace surface in the lungs of normal adults (col. 4, lines 3-33).

Mautone describes the process of preparing lipid crystals in combination with a therapeutically active substance comprising: preparing a mixture of one or more lipids of the group of phospholipids known as phosphatidylcholines and one or more spreading agents, in powder form, and said therapeutically active substance and one or more fluorocarbon propellants (col. 5, lines 5-42). The major lipid component is the phospholipid 1,2dipalmitoyl phosphatidylcholin (DPPC) which is the most surface active of the phospholipids. Another minor lipid component that acts as a spreading agent for the major component can be diacylphosphatidylglycerol (PG) (col. 6, lines 4-68). Aerosolized drug delivery systems and the method of making them are described in

examples I-VI. The administration of the aerosolized drug delivery system and the device are explained in columns 10 and 11. Mautone lacks specific disclosure on high doses of phospholipids in the formulation.

Rubin teaches aerosolized surfactants for treatment of airway obstruction. Addition of a hypersmolor drug will help to minimize mucus in the airway. The surfactant can also be used as the distributing agent for other medications throughout the airways. Rubin discloses studies conducted on patients with a diagnosis of asthma and other active pulmonary diseases (col. 3, lines 55-65), where the surfactant preparation used was Exosurf®. Patients received one of three different doses of 202.5, 607.5 or 1215 mg DPPC per day. Study drug was administered as an aerosol using a jet nebulizer three times a day (col. 4, lines 5-42).

Rubin concludes that an important determinant of the effects of exogenous surfactant is its ability to spread into the airway. From the clinical results obtained, it is speculated that 607.5 mg DPPC per day achieved coverage of the conductive airways to saturation. However, in vitro analysis of sputum clearance showed a dose-related effect (col. 8, lines 4-15). Rubin therefore discloses use of surface-active agents to promote mucus clearance, especially dipalmitoyl-phosphotidylcholine (DPPC), which may be administered to airways by metered dose inhalation, dry powder inhalation, jet nebulization and ultrasonic nebulization (col. 9, lines 28-45).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the preparations of Radhakrishnan by adding the component ratios as taught by Mautone, and because Mautone teaches that the liposome preparations can be administered with or without a drug. Also because of the disclosed benefits of the lung surfactants in respiratory disorders and in carrying drugs into the lung. It would also be a logical extension of the combined teachings to prepare the formulations as a combined product, such as a pack and to include patient instructions for proper administration and use. Furthermore, it would have been obvious to one of ordinary skill in the art, given the teachings of the combined references on lower dosages of the phospholipids, to have looked in the art for higher doses, as taught by Rubin, in order to obtain more effective results, especially since Radhakrishnan teaches that effects of liposomes are dose-related.

Response to Arguments

Applicant's arguments filed 04/07/03 have been fully considered but they are not persuasive. Also, the applicant's amendments necessitated a new grounds of rejection (using one additional prior art).

Applicant argues that Radhakrishnan teaches use of liposomes in suspensions to "provide improved controlled release in terms of reduced rapid systemic drug uptake", thus providing a structure that will release a drug only slowly at a controlled rate. This is not the correct interpretation of Radhakrishnan's teaching. Radhakrishnan teaches methods of administering a drug, at a selected dose, via the respiratory tract, and he

uses liposomes to deliver the drug. He teaches how, using liposomes can assist in controlling the rate of the drug release in the respiratory tract. Radhakrishnan reads " the inventions mentioned above show that liposome drug delivery by inhalation provides advantages of (a) reduced side effects due to **rapid systemic drug uptake**, (b) improved therapeutic action over an extended period, and (c) the ability to modulate **rate** of drug release from the target site" (col. 3, lines 42-47). Generally, "ability to modulate rate" is not interpreted as SLOW drug release. In column 5, lines 5-20, Radhakrishnan teaches that the liposome component of the formulation effects the drug release rate and states a range of from 0.5 hour to nearly 10 days.

Applicant argues that Radhakrishnan and Mautone references in contrast and one skilled in the art would not be motivated to combine them. However, 1) as shown above Radhakrishnan is not teaching slow release, therefore there is no contrast. 2) even if the reference of Radhakrishnan was concerned with slow release, its teachings were not considered teaching away from that of Mautone, therefore it would be appropriate for the office to combine these two references. It is noted that the instant claims are drawn to a "product", and the rate of release of the drug is not a concern or point of novelty. When the components of the "product" are taught by prior art, it is considered met.

Applicant states that modifying the teachings of Radhakrishnan by using the component ratios of Mautone is not obvious. This is not persuasive because Radhakrishnan is clearly teaching combination of liposomes (see for example, col. 5).

Thus it would be obvious to one of ordinary skill in the art to look for appropriate ratios of the components in other arts.

Applicant argues that Mautone is teaching that "liposomes enter cells rather than spreading", and that "Mautone itself clearly teaches against combination with compositions such as those in Radhakrishnan". This is incorrect interpretation of Mautone's disclosure. Column 3, lines 35 to 44 should be read as one disclosure. It reads "the liposomes have been formulated as vehicles to carry medications into lungs. The liposomes are essentially a lipid membrane-bound spherical vesicle, **analogous** to intracellular organells.....their probable mode of action is by adsorption or fusion to the cell surface, whence either the contents may be liberated and enter the cell...". It is understood that it is the "intracellular organells" that enter the cells and not the liposomes. Mautone is clearly teaching "spreading agents" which assist in spreading the liposome on the surface of the lung.

Applicant argues that Radhakrishnan "does not recognize any therapeutic effect contributed by the lipid components of their liposomes, the lipids being present only to provide a delivery vehicle". This is not commensurate with the scope of the claims. The instant claims are drawn to "a product" comprising a medicament and one or more liposomes. Radhakrishnan teaches exact same product. Also noted that components or agents will behave the same in the same environment, regardless of it is given title. Thus, if liposomes can behave actively on the surface of the lungs in one formulation, they can do so in other formulations too.

Applicant argues that Mautone does not teach or suggest "how to limit the 80 to 20 ratios in regard to any particular sub-set of components". This is not persuasive. Mautone is clearly teaching that the formulation contains between 80 to 99.5 percent by weight and the spreading agent, (which is the second lipid component) in amount of about 0.5 to 20 percent by weight. It is clear to one of ordinary skill in the art that, for example, a ratio of 80:20 is taught by Mautone.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 703-308-6330. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose Dees can be reached on 703-308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

MICHAEL G. HARTLEY
PRIMARY EXAMINER

Mina Haghighatian
June 13, 2003